

Remarks

Claims 12-14, 44, and 45 were pending in the subject application. By this Amendment, claim 12 has been amended, claims 13 and 14 have been cancelled, and new claim 46 has been added. The undersigned avers that no new matter is introduced by this Amendment. Support for the new claims and amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 12 and 44-46 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 CFR §1.114 for the subject application.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. Applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

By this Amendment, claim 12 has been amended and claim 46 has been added. Support for the amendment to claim 12 can be found, for example, at page 15, lines 28-32; page 25, lines 17-26; Examples 4 and 5 at pages 47-48; page 49, lines 10-15; and the abstract of the specification, and claim 14 as originally filed. Support for claim 46 can be found, for example, at page 13, lines 25-27, of the specification.

Claims 12-14, 44, and 45 remain rejected under 35 USC §103(a) as obvious over McSwiggen *et al.* (U.S. Patent No. 5,693,532) in view of Tuschl *et al.* (U.S. Patent Publication 2004/0259247) and Chen *et al.* (U.S. Patent Publication 2004/0242518). Applicants respectfully traverse.

The McSwiggen *et al.* patent is cited in the Office Action for teaching methods of inhibiting the replication of RSV using ribozymes targeted to RSV NS1 and NS2 targets. The Tuschl *et al.* publication is cited for teaching that siRNAs provide greater gene silencing activities than ribozymes. The Examiner's rationale for the rejection appears to be based on the substitution of one known equivalent element (ribozymes) for another (siRNA) to obtain predictable results. However, the combination of the references cited in the Office Action does not yield predictable results. At

page 3 of the Office Action, the Examiner acknowledges that the McSwiggen *et al.* patent does not teach administration of NS1-targeted ribozymes to a subject not suffering from RSV infection. By this Amendment, Applicants have amended claim 12 to recite that the subject does not have an RSV infection at the time the vector is administered. The Chen *et al.* publication is cited in the Office Action for teaching the use of siRNA expression vectors to inhibit viral infection in human lungs, and for exemplifying the use of siRNA expression vectors to prophylactically inhibit influenza infection in the mouse lung. Specifically, in the paragraph bridging pages 4 and 5, the Office Action states:

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the siRNA expression vectors to a subject not suffering from RSV infection in order to prevent infection, and would have had a reasonable expectation of success in view of the results of Chen who showed that expression of anti-influenza siRNAs prior to infection decreased the titer of subsequently infecting influenza virus.

All respiratory infections are not the same and influenza infection is not the equivalent of RSV infection. RSV infection has its own pathogenesis. Although the Chen *et al.* publication does demonstrate the use of siRNA expression vectors to prophylactically inhibit influenza infection and reduce viral titer in the mouse lung by inhibition of influenza nucleoprotein (NP) and polymerase basic (PB) protein expression, this does not correlate with or confer a reasonable expectation of success in prophylactically reducing RSV titer by inhibition of NS-1 expression. “[A] patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. ...[I]nventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” *KSR Intern. Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, at 1741. In the current rejection, the Examiner is extrapolating from prophylaxis with NP and PB in influenza to a different gene (NS1) in a different virus (RSV), without any scientific basis.

It should also be considered that the primary reference, the McSwiggen *et al.* patent, contains no empirical data, *in vitro* or *in vivo*, demonstrating that NS-1 targeting ribozymes, or any nucleic acid inhibitor, can be prophylactically delivered to airway cells *in vivo* such that expression of the RSV gene or transcript in the airway cells and RSV titer in the subject are reduced. Example 2 of

Tuschl *et al.* demonstrates gene silencing in mammalian cells *in vitro*; however, there is no empirical evidence in the cited references that the siRNAs can be prophylactically delivered to airway cells *in vivo* such that expression of the RSV gene or transcript in the airway cells and RSV titer in the subject are reduced. The cited references and the Office Action do not establish a correlation between the disclosed procedures and reduction in RSV viral titer in the human airway.

Without having the benefit of this empirical data at the time the application was filed, one of ordinary skill in the art would not have a reasonable expectation of success in carrying out the method of the invention, which includes reduction of RSV gene expression and RSV viral titer in a human subject by prophylactic administration of the vector. It was the inventors of the subject application that determined that inhibition of RSV NS1 gene expression in interferon (IFN)-deficient Vero cells did not attenuate RSV infection, suggesting a role of the NS1 protein in the promotion of RSV infection by inhibiting the type-1 IFN pathway (see Example 1 at page 45 of the specification). The inventors verified that NS1 decreases the amount of type-1 IFN by immunoblotting, microarray analyses, and translocation experiments (see Example 2 at pages 45-46 of the subject specification). The data disclosed herein describe the significant role of NS1 in RSV replication and immunity to RSV infection. These studies demonstrate that the NS1 protein down-regulates the IFN-signaling system by deactivation of STAT1, IRF1, and IFN-regulated gene expression, which are critical to suppressing IFN action (Example 6, pages 48-52 of the subject specification).

Citing priority application no. 60/481,738 and the Bossert *et al.* (2002) publication, the Office Action indicates that “one of ordinary skill in the art at the time of the invention would have had reason to expect that inhibition of RSV NS1 expression would have relieved RSV inhibition of host interferon activity, leading to a reduction in titer” and that “such an increase in host immune response against RSV due to NS1 inhibition would not necessarily have been unexpected” (pages 7 and 8 of the Office Action).

Applicants submit that the observation that RSV NS1 somehow plays a role in interfering with interferon response does not confer a reasonable expectation that inhibiting NS1 expression by prophylactic administration of an NS1-targeted RNA interference molecule would reduce RSV titer *in vivo*. It should be noted that the Bossert *et al.* (2002) publication describes an *in vitro* study using cell lines. At page 4291, the Bossert *et al.* publication itself indicates that how interferon resistance is

mediated by the RSV NS1 proteins was not yet known. Not all of the cells in the host's respiratory system that mediate the interferon response are infected by RSV. Although Bossert *et al.* observed that NS1 and NS2 provided resistance to interferon-mediated antiviral response and that both NS1 and NS2 were required for this effect *in vitro*, there is no indication as to whether both proteins would be required *in vivo*. Without empirical data *in vivo*, the effects of inhibiting NS1 expression *in vivo* are speculative in nature, such that one of ordinary skill in the art could only suppose that "NS1 might improve the cellular immune response and result in a decrease in viral titer" (Office Action, page 7).

At the time the subject application was filed, the cited references would not have conferred a reasonable expectation of success in delivering a vector comprising a nucleic acid sequence encoding an siRNA to airway cells in a human *in vivo*, such that expression of a targeted RSV NS1 gene or transcript and RSV viral titer are reduced. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. MPEP §2143.01. Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); MPEP §2143.02.

As described in Examples 4 and 5 at pages 47-48 of the specification, when administered two days before or two days after inoculation with RSV, a complex of chitosan and siRNA plasmid (NG042-siNS) targeting RSV NS1 was effective in reducing RSV NS1 expression and reducing RSV titers. Furthermore, lung sections of mice treated two days after RSV infection exhibited a significant decrease in lung inflammation.

Submitted with Applicants' previous Amendment was the Zhang *et al.* publication (*Nature Medicine*, 2005, 11:56-62), a scientific publication co-authored by the inventors of the subject application. As described at page 52 of the subject specification and the Discussion section of Zhang *et al.*, the results of the inventors' studies on the prophylactic potential of NG042-siNS1 indicate that the NS1-targeted siRNA induces substantial protection from RSV infection, infection-induced inflammation, and airway reactivity, and the protective effect lasted for at least four days. Furthermore, even a single-dose prophylaxis considerably inhibits re-infection in mice that are

administered a higher dose of RSV sixteen days after primary infection. Without being bound by theory of mechanism, the inventors propose that NS1 gene knockdown confers enhanced protection by augmenting the anti-RSV host immunity via enhanced IFN production, which prevents mice from RSV re-infection. As RSV is a major cause of respiratory illness in young children and the immunocompromised, and previous RSV infections do not prevent subsequent infections, these results are of practical significance. Applicants respectfully submit that these results are unexpected in view of the references cited within the Office Action, particularly in view of the lack of empirical results contained within the cited references.

Accordingly, reconsideration and withdrawal of the rejection under 35 USC §103(a) is respectfully requested.

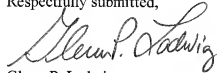
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Glenn P. Ladwig
Patent Attorney

Registration No. 46,853

Phone No.: 352-375-8100

Fax No.: 352-372-5800

Address: Saliwanchik, Lloyd & Eisenschenk
A Professional Association
P.O. Box 142950
Gainesville, FL 32614-2950

GPL/jnw

Attachments: Request for Continued Examination
Supplemental Information Disclosure Statement